REMARKS

A. Status of the Claims

Prior to the submission of this paper, claims 1-28, 30, 31, 33-67, 73, 76-99, 105-109, and 111-125 were pending in this application, with claims 2-23, 28, 30, 31, 36-67, 74, 78-98, 109, 111-113, 118, and 122 withdrawn from consideration. In this paper, Applicants have requested the cancellation of claims 1-23, 34, 36-67, 73, 76-99, 118-121, and 125 without prejudice or disclaimer. When these claim cancellations have been entered, the claims under examination will be claims 24-27, 33, 35, 105, 107, 108, 111-112, 114-117, and 122-124. Claims 28, 30, 31, 109 and 113, though withdrawn from consideration, have not be cancelled and are still pending.

Claims 1, 24-27, 33-35, 99, 105-108, 114-117, 119, 121, and 123-125 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent No. 6,573,299 to Petrus ("Petrus") in view of an abstract of an article entitled "Connective tissue biochemistry of the aging dermis. Age-related alterations in collagen and elastin", by J. Uitto, Dermatol. Clin. 1986 Jul; 4(3):433-46 ("Uitto").

B. Explanation of the Amendments

Claims 24, 35, 105, 115-117, 123, and 124 have been amended to specify various zinc concentration ranges. Support for these amendments is found in Example 1 and ¶[39] of the originally filed specification.

Independent claims 24 and 105 have been amended to specify that the claimed method is for increasing elastin "in a region of skin of a subject". Support for this amendment is

found throughout Applicants' originally filed specification [e.g., see ¶[23], Figures 7-11 and corresponding text]. Independent claims 24, 105, and 115 have been amended to specify that "the elastin content in the area of skin is increased in a sufficient amount to treat or to prevent wrinkles." Support for this amendment is found in ¶[23] of the originally filed specification, as well as in Figures 7-11 and their corresponding text.

C. Applicants Claims Are Patentable Over the Cited References

Applicants respectfully traverse the rejection of claims 24-27, 33-35, 105-108, 111-112, 114, 115-117, and 122-125 under 35 U.S.C. § 103(a), for allegedly being unpatentable over Petrus, in view of Uitto.[1] In this paper, the arguments focus primarily on Petrus, as Uitto is recited only for the alleged teaching that loss of elastin is related to wrinkle formation.

1. Petrus Teaches Away from the Claimed Ranges

As noted in Applicants' previous response, Petrus is directed to treating disorders associated with the aging eye. Petrus asserts that a primary cause of these disorders is inflammation, stating that "[i]nflammation accelerates the aging process and is believed to be responsible for many of the changes that occur in the aging eye" [Petrus, col. 9, lines 29-31]. To prevent or to treat such conditions, Petrus suggests the use of seven classes of anti-inflammatory compounds, which include zinc compounds [Petrus , col. 8, line 45 to col. 14, line 34]. Petrus characterizes zinc compounds as "anti-inflammatory" [Petrus, col. 12, lines 10 and 44] and notes

[1] Applicants' only address the rejection of claims 24-27, 33, 35, 105, 107, 108, 111-112, 114-117, and 122-124., as these are the only claims still under examination following the claim cancellations requested herein.

that zinc may be used to inhibit nitric oxide synthase (NOS) expression through the suppression of proinflammatory cytokines " [Petrus, col. 13, lines 16-17, col. 7, lines 51-53]. To inhibit NOS expression, Petrus states that "[t]he suggested [zinc] topical dosage range of the present invention is 10 to 20 mg per day" [Petrus, col. 13, lines 19-21]. This dosage range was determined by Applicants to correspond to topical compositions which have zinc concentrations higher than Applicants' claimed range [see Applicants' March 30, 2007 paper, pp 34-35]. Furthermore, Petrus teaches that "zinc is virtually non-toxic" [Petrus, col. 12, line 53]. Based on these observations, Applicants argued that one of ordinary skill in the art would, if anything, seek to ***increase*** the concentration of zinc in topical compositions in order to treat the inflammation associated with disorders of the aging eye.

The Examiner disagrees, stating that "Applicant is inferring a conclusion that is not explicitly, or even implicitly, stated in the disclosure of Petrus" [Office Action, p. 5, lines 12-13]. However, the Office Action's analysis is flawed, because it fails to consider the teachings of Petrus in their entirety. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) (stating that, in assessing obviousness, one must consider what the combined teachings of the references would have suggested to those of ordinary skill in the art). Petrus reports that disorders of the aging eye are caused by inflammation and that zinc compounds treat inflammation [Petrus, col. 9, lines 29-31; col. 12, lines 10 and 44]. Petrus further reports that "zinc is virtually non-toxic" [Petrus, col. 12, line 53]. In view of these statements, one of ordinary skill in the art would have easily deduced that formulations containing high zinc concentrations would be beneficial. Thus, one of ordinary skill in the art would not have sought to use formulations with low

concentrations of zinc, and would not have arrived at Applicants' invention. In other words, Petrus teaches away from the low zinc concentration ranges claimed by Applicants.

The Office Action attempts to negate these clear teachings of Petrus by relying on the following passage of Petrus, which purportedly teaches to vary the concentration of bio-affecting agents:

> [t]he concentration of the bio-affecting agents in the composition can also vary greatly and will be dependent upon many factors, e.g., type, bioavailability, potency, surface area to which it is applied, composition used, and the amount of the penetrating agent used." [Office Action, p. 5, lines 16-19].

However, a consideration of these factors would lead one of ordinary skill in the art to ***increase*** the zinc concentration of a topical formulation, not decrease it. For instance, the first factor, which is "type", refers to the type of bio-affecting agent, which in this case is a zinc compound [see Petrus, col. 12, line 10 - col. 13, line 42]. Because Petrus reports that zinc is "virtually non-toxic" and fights inflammation associated with aging eye disorders [Petrus, col. 9, lines 29-31; col. 12, lines 10 and 44], this factor would suggest the use of compositions with a high concentration of zinc.

The second and third factors, which are "bioavailability" and "potency", also would lead suggest compositions with a high concentration of zinc. Petrus reports a suggested dosage of zinc compound of 10 - 20 mg / day, which, as noted above, was determined by Applicants to correspond to topical compositions which have zinc concentrations significantly higher than Applicants' claimed range. If the bioavailability or potency of the zinc compounds in these topical compositions were to be less than 100%, the zinc compound would have to be

present in the topical composition at an ***even higher*** concentration in order to reach the suggested dosage of Petrus.

The fourth factor, which is a consideration of the "surface area to which the [bio-affecting agent] is to be applied", also would not provide any motivation to decrease the zinc concentration levels in a topical formulation. As the skilled artisan will appreciate, if a bio-affecting agent is toxic, the size of the surface area to be treated with a topical composition containing the bio-affecting agent will dictate the maximum concentration of a bio-affecting agent in the composition. In other words, an acutely toxic bio-affecting agent would have to be present in low concentration in a topical composition intended for treating a large surface area of the skin of patient. Otherwise, systemic poisoning could result from the topical application of the composition. In this case, however, Petrus states that "zinc is virtually non-toxic" and the area to be treated (i.e., the eye and eyelids) is small. Thus, the skilled artisan would seek to use a high concentration of zinc in a topical composition, since a higher concentration would be presumed to be more efficacious, without any toxic side effects.

The fifth and sixth factors, which are "composition used" and "amount of penetrating agent used" also would not provide motivation to use a low concentration of zinc compound in a topical composition. As noted above, Petrus's suggested daily topical dosage of zinc compound is 10 - 20 mg / day, which corresponds to topical compositions which have zinc concentrations higher than Applicants' claimed range. If the topical composition or the amount of penetrating agent were insufficient to provide for 100% delivery of the zinc, then the zinc compound would have to be present in the topical composition at an ***even higher*** concentration in order to reach the suggested dosage of Petrus. Thus, even if a passage in Petrus teaches that

the amount of bio-affecting agent can be varied, the combined teachings of Petrus would motivate the skilled artisan to ***increase*** the zinc concentration. For these reasons, Applicants maintain that Petrus teaches away from the claimed invention.

2. The Office Actions' Reliance on "Standard Medical Practice" To Arrive at the Claimed Invention Is Inconsistent with Commercially Available Topical Zinc Products

The Office Action attempts to rely on "standard medical practice" to rebut Applicants' observation that Petrus teaches away from the claimed low zinc concentration ranges. According to the Office Action, "the idea that the artisan would only be motivated to increase the dosage amount of active zinc compound based upon the anti-inflammatory and nitric oxide synthase-inhibiting effects is disputed in light of standard medical practice" [Office Action, p. 6, lines 1-3]. The Office Action warns that "the idea that the artisan would have gratuitously increased the effective amount of the active agent just because it has demonstrated a beneficial therapeutic effect at a particular concentration disregards the fact that excessive concentrations of any pharmacologic therapy will result in notable, if not severe and/or fatal side effects." [Office Action, p. 6, lines 5-8]. To support these statements, the Office Action describes serious and potentially life-threatening side effects associated with overdosing on aspirin [Office Action, p. 6, lines 9-11].

The Office Action's analogy to aspirin is inappropriate, as Applicants do not dispute that drugs can possess toxic side effects that can be lethal, especially with an overdose. However, Applicants' claims relate to topical zinc compositions, and Petrus, which is the Office Action's primary reference, states that zinc is"virtually non-toxic". Furthermore, the Office

Action's conclusions seem to imply that formulations with zinc concentrations higher than those of Petrus would have been recognized as dangerous by one of ordinary skill in the art. However, those conclusions are not supported by an analysis of the zinc content in other topical zinc formulations for treating inflammation. For example, Zincofax is a topical zinc oxide diaper cream for treating the inflammation and redness associated with diaper rash. The original formula, which has been available since 1945, contains 15% zinc oxide. Later formulations contain either 15% zinc oxide (fragrance free formula) or 40% zinc oxide (extra strength formula) [see Zincofax product literature that accompanies this response]. On a concentration basis, the respective zinc concentrations are about 1.9 mol/liter [original and fragrance free formulas] or 4.9 mol/liter [extra strength formula]. Thus, the zinc concentrations in all of the Zincofax formulations are orders of magnitude above Applicants' claimed range of zinc concentrations. Moreover, as the Examiner will appreciate, Zincofax, like all diaper creams, are typically applied several times a day (e.g., with each diaper change) in order to treat and cure the inflammation and redness associated with diaper rash. In view of this repetitive use of concentrated topical zinc formulations such as Zincofax, one of ordinary skill in the art, at the time this application was filed, would have sought to use the higher concentrations of zinc in Petrus's compositions, in order to treat the inflammation associated with disorders of the aging eye. Certainly, there would have been no motivation to use the extremely low concentrations of zinc recited in Applicants' claims.

3. The Office Action's Engages in Improper Hindsight in Relying on the Petrus's Statement that the Bioaffecting Agents can be Present at a "Concentration of 0.1 - 40 %"

The Office Action asserts that Applicants' claimed invention is obvious in view of a general statement in Petrus that the concentration of bio-affecting agents, including zinc compounds, can be varied "from about 0.1% to 40% of the total composition" [Office Action, col. 6, lines 60-62]. According to the Office Action, this general statement provides a teaching to prepare compositions with zinc concentrations anywhere between 0.1% to 40%, including at zinc concentrations within the ranges recited in Applicants' claims. [Office Action, p. 7, lines 12 to p. 8, line 7].

The Office Action's analysis is flawed, because a skilled artisan would not have interpreted that the full "0.1% to 40%" concentration range would be applicable to all of the hundreds of bio-affecting agents reported in Petrus. For instance, Petrus reports that beta hydroxy acid (i.e., salicylic acid) can be a "bio-affecting agent" [Petrus, col. 6, lines 49-50]. However, salicylic acid is a severe eye irritant (see accompanying MSDS of salicylic acid). Accordingly, one of ordinary skill in the art would not prepare a 40% salicylic acid composition for the treatment of wrinkles around the eye, even if Petrus describes a concentration range of 0.1% to 40% for bio-affecting agents.

Similarly, one of ordinary skill in the art would not have viewed the "0.1% to 40%" concentration range as a teaching to prepare topical compositions with a zinc concentration of 0.1%. There is no teaching or suggestion anywhere in the art of record that any effect, beneficial or otherwise, can be observed by using zinc at a concentration of 0.1%. To the contrary, Petrus reports dosages which would correspond to compositions with high zinc

concentration, as noted above. Moreover, the high zinc concentrations in Zincofax, which was available at the time this invention was made, would have suggested to one of ordinary skill in the art that the operable range of zinc concentrations is towards the high end of the "0.1% to 40%" concentration range.

Given the hundreds of bio-affecting agents reported by Petrus and the potential for each of these bio-affecting agents to have its own operable sub-range within the broad 0.1% to 40% range, the Office Action's proposal to prepare a 0.1 % zinc citrate composition is based on nothing more than hindsight reasoning. In this respect, the situation is analogous to that in Ex parte Garvey, 41 USPQ 583, at 584, which states that

> [t]he likelihood of producing a composition such as here claimed from a disclosure such as shown by the [cited reference] would be about the same as the likelihood of discovering the combination of a safe from a mere inspection of the dials thereof." [Garvey, at 584 (emphasis in the original).]

The Office Action attempts to justify its hindsight reasoning by referring to MPEP §2123, stating that "[a] reference may be relied upon for all that it would have ***reasonably suggested*** to one having ordinary skill in the art, including non-preferred embodiments…Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments." [Office Action, p. 7, lines 3-6 (emphasis added)]. However, the Office Action's analysis misses Applicants' point, which is that, ***as a matter of law***, a reference ***does not reasonably suggest*** an embodiment if one can only arrive at the embodiment by selecting from a large number of possibilities. See In re Luvisi 52 C.C.P.A. 1063, 1068 [stating that compositions that are a "needle-in-a-haystack" with respect to the prior art are not obvious over

the prior art.], See also Ex parte Garvey, 41 USPQ 583, 584. The Office Action's reasoning continues to ignore this body of case law, without any justification or authority.

The Office Action also attempts to justify its hindsight reasoning by relying on Petrus's alleged teaching to vary the concentration of a bio-affecting agent. According to the Office Action, a teaching to vary the concentration of the bio-affecting agent is sufficient to suggest preparation of a 0.1% zinc citrate composition [Office Action, p. 7]. However, as discussed in detail above, one of ordinary skill in the art, upon reading the cited passage in Petrus [i.e., col. 6, lines 56-60], would have been motivated to ***increase*** the zinc concentration of a topical formulation, based on a consideration of the type of bio-affecting agent, bioavailability, potency, and other factors specifically recited by Petrus. Thus, the ***combined teachings*** of Petrus suggest topical formulations with high zinc concentration. The mere recitation of a general concentration range of 0.1 % to 40% for bio-affecting agents is insufficient to overcome these combined teachings of Petrus, which teach away from the claimed invention. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) (stating that, in assessing obviousness, one must consider what the combined teachings of the references would have suggested to those of ordinary skill in the art)

4. Applicants' Claimed Concentration Ranges Are Fully Enabled and Produce Unexpected Results

In rejecting Applicants' claims for allegedly being obvious, the Office Action appears to suggest that Applicants have not enabled the full scope of the claimed ranges According to the Office Action,

> Applicant has not provided any objective evidence, scientific reasoning, or persuasive argument on the record to provide an adequate basis for concluding that exemplary data in the instant specification was somehow probative of the same (or at least substantially similar) effect using the elected subject matter *over the full scope of dosage amounts instantly claimed*. [Office Action, p. 11, lines 15-18 (emphasis in the original)]

Without agreeing to the propriety of this rejection, Applicants have amended the claims to recite zinc concentrations that range from 10 μM to 10 mM. As discussed in the accompanying Declaration under 37 C.F.R. §1.132 by Dr. Jacob Waugh, Applicants have performed additional experiments using zinc citrate, the currently elected species, as a Zn ion source for topical formulations containing 1 μM, 1.0 mM, 10 mM and 1 M Zn. The experiments involve applying these formulations onto the skin of live mice for a fixed period of time, harvesting the skin, and examining the skin for signs of increased elastin [Waugh Declaration, ¶¶ 7-11]. The results show that the formulations containing Zn at concentrations of 1 μM, 1.0 mM, and 10 mM induced the formation of elastin in murine skin without irritation and sloughing [Waugh Declaration, ¶ 7]. Application of the 1 M formulation, however, did not result in a net gain of elastin [Waugh Declaration, ¶¶ 9-11]. Instead, skin irritation was observed [Waugh Declaration, ¶ 9]. The lack of elastin formation after application of the 1 M Zn formulation was attributed to increased elastase activity, which Applicants have discovered to occur at high zinc concentrations [see, e.g., original specification, Example 9]. Applicants have also demonstrated that increased elastin results from topical application of a 100 mM Zn solution, although irritation and sloughing occur [original specification, Example 1].

Since Applicants have demonstrated experimentally that increased elastin production occurs in the range of 1 μM to 10 mM without irritation or sloughing, Applicants

submit that the Zn concentration range from 10 μM to 10mM, which is broadest zinc concentration range presently claimed, is fully enabled.

5. A Direct Comparison Between Applicants' Claimed Invention And Petrus Confirms The Non-obviousness of Applicants' Invention.

In rejecting Applicants' claims, the Office Action has requested that Applicants compare the claimed invention to Petrus in order to demonstrate that the claimed invention provides unexpected activity over Petrus [Office Action, p 11]. . As set forth below, Petrus does not recognize the critical zinc concentration ranges recited in Applicants' claims. Accordingly, Applicants' claimed ranges are not obvious over Petrus.

Petrus reports that numerous zinc compounds may be used in its formulations, including zinc sulfate, zinc chloride, zinc acetate, zinc carbonate, and zinc oxide. While Petrus reports that the suggested daily dose is 10 - 20 mg [Petrus, col. 13, lines 20], Petrus does not teach or disclose a zinc concentration range for its formulations. The only instances where Petrus describes the zinc compounds in terms of a concentration are in Examples 1 and 2, which report a topical gel or cream containing 2% zinc lineolate.

As all concentrations mentioned in Petrus are in terms of a percentage, Applicants adopted Petrus's target concentration of 2.0 % for zinc compounds and calculated the corresponding molar Zn concentrations for zinc sulfate, zinc chloride, zinc acetate, zinc carbonate, and zinc oxide. The results, shown below, indicates that in each case the corresponding molar concentration of zinc is above 100 mM:

Zinc Source (Petrus)	**Zn Concentration in 2.0% Formulation (in mM)**
Zinc sulfate	124
Zinc chloride	148
Zinc acetate	110
Zinc carbonate	160
Zinc Oxide	246

This result is significant, because Applicants previously showed that topical application of compounds with a zinc concentration greater than 100 mM leads to irritation and sloughing [see original specification, Example 1]. Thus, topical application of a formulation containing 2.0% zinc sulfate, zinc chloride, zinc acetate, zinc carbonate, or zinc oxide, as suggested by Petrus, would lead to irritation and sloughing. Petrus does not recognize these effects at all, and, to the contrary, report that zinc is "anti-inflammatory" [Petrus, col. 12, lines 10 and 44]. Thus, Petrus does not recognize, teach or suggest the critical zinc concentration ranges recited in Applicants' claims.

6. Applicants' Product Continues to Win Industry Accolades

For two consecutive years, Applicants' commercial product, Relastin Eye Silk, has won Allure Magazine's Editor's Choice "Best of Beauty" Award in the category of "Antiwrinkle Eye Creams". Applicants' previous paper reported that Relastin Eye Silk was

named the best "Antiwrinkle Eye Cream" of 2007. Here, Applicants report that Relastin Eye Silk has been named best "Antiwrinkle Eye Cream" of 2008 [see attached article].

As reported by the Wall Street Journal, these industry accolades garnered by Applicants' commercial product involve testing by cosmetic chemists and dermatologists [see accompanying WSJ article]. Allure Magazine reports that "[w]e tested thousands of beauty products to find our 182 undisputed champions." [Allure Magazine, October 2008 issue, p. 272]. Thus, these awards are based on the performance of the product, rather than a clever marketing campaign or volume of gross sales. Allure Magazine states that "Relastin Eye Silk is ***amazing at building elastin***" [Allure Magazine, October 2008 issue, p. 288 (emphasis added)].

The performance of Relastin Eye Silk can be directly attributed to the benefits obtained by practicing the presently claimed invention. As discussed in the accompanying declaration by Dr. Jacob Waugh, Relastin Eye Silk contains the following ingredients: cyclopentasiloxane, dimethicone crosspolymer, dimethicone, phenoxyethanol, zinc complex, mica, and titanium dioxide [Waugh Declaration, ¶ 14]. According to Dr. Waugh, the zinc complex is the only component that would be expected to increase the production of elastin [Waugh Declaration,¶ 17]. The zinc complex is one of the presently claimed zinc-containing substances and is present in the formula to provide zinc at a concentration that falls within the presently claimed concentration ranges [Waugh Declaration, ¶¶15-17]. The remaining ingredients would not be expected to have any effect on the body's ability to product elastin [Waugh Declaration, ¶¶ 15, 17]. For instance, cyclopentasiloxane, dimethicone crosspolymer, and dimethicone are organosilicon polymers that provide the requisite consistency for the cream product [Waugh Declaration, ¶ 15]. Phenoxyethanol is a well known cosmetic preservative

[Waugh Declaration, ¶ 15]. Mica and titanium dioxide are minerals that improve the appearance and luster of the product [Waugh Declaration, ¶ 15].

In view of the foregoing, there is a direct nexus between the industry accolades garnered by Relastin Eye Silk and the presently claimed invention. The accolades are based on product performance which can be directly traced back to practicing the claimed methods of increasing elastin by topical application of compositions containing zinc in specified concentration ranges. Accordingly, these two consecutive awards provide strong secondary indications that the claimed invention is not obvious.

CONCLUSION

Applicants arguments and evidence provided here clearly demonstrate that Petrus fails to teach or suggest Applicants' claimed invention, which uniquely and unexpectedly increases elastin formation in order to treat and to prevent wrinkles. Not only does Petrus teach away from the low concentration ranges claimed by Applicants, the evidence provided by Applicants demonstrate that the higher doses within the scope of Petrus are inapplicable and undesirable. Finally, the accolades bestowed on Applicants' product further demonstrate the unique and unexpected qualities provided by Applicants' claimed invention. Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 103720-105089US1. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 103720-105089US1.

Respectfully submitted,
KING & SPALDING, L.L.P.

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